AWARD NUMBER: W81XWH-14-2-0170

TITLE: A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function, and Cardiometabolic Profiles in Persons with SCI

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CONTRACTING ORGANIZATION: Bronx Veterans Medical Research Foundation, Inc.
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

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14. ABSTRACT

This clinical trial is designed to demonstrate that the walking skills achieved in the preliminary study at the JJPVAMC can be achieved in a larger sample of participants and at three study sites. It is also designed to determine if the body composition and bowel function benefits that were observed with as few as four to six hours per week of walking over three months can be demonstrated in a larger sample. The Phase II trial conducted at the JJPVAMC demonstrated that ten participants were able to use the device to successfully walk for four to six hours per week for three months. It is unknown if a larger sample of persons with SCI can be taught to walk in these devices with a similar proficiency and competence as demonstrated in our pilot study. As such, the primary objectives of this proposal are to achieve successful walking skills in the exoskeletal-assisted walking devices for an extended period of time and at specific velocities and distances over the course of 36 sessions in three months in people with chronic SCI who are wheelchair dependent for community mobility. The secondary objectives are to determine if this amount of walking is effective in improving bowel function and body composition in the same patient population. The exploratory objectives are to address additional questions concerning the retention or non-retention of the positive changes, the effects of the increased physical activity from exoskeletal-assisted walking (WALK) on vagal tone, orthostatic tolerance, lipid profile, total testosterone, estradiol levels, and quality of life (QOL). Other tertiary goals are to explore the relationships among these variables. 14 participants have been randomized across 3 sites thus far, with the first anticipated participant completion being January of 2016.

15. SUBJECT TERMS

Exoskeletal Assisted Walking (EAW), Spinal Cord Injury (SCI), HDL-c, Lipid profile, Orthostatic tolerance, total cholesterol, estradiol, quality of life (QOL), ReWalk, Ekso

16. SECURITY CLASSIFICATION OF:	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Table of Contents

Page

Introduction

This clinical trial is designed to demonstrate that the walking skills achieved in the preliminary study at the JJPVAMC can be achieved in a larger sample of participants and at three study sites. It is also designed to determine if the body composition and bowel function benefits that were observed with as few as four to six hours per week of walking over three months can be demonstrated in a larger sample. The Phase II trial conducted at the JJPVAMC demonstrated that ten participants were able to use the device to successfully walk for four to six hours per week for three months. It is unknown if a larger sample of persons with SCI can be taught to walk in these devices with a similar proficiency and competence as demonstrated in our pilot study. As such, the primary objectives of this proposal are to achieve successful walking skills in the exoskeletal-assisted walking devices for an extended period of time and at specific velocities and distances over the course of 36 sessions in three months in people with chronic SCI who are wheelchair dependent for community mobility. The secondary objectives are to determine if this amount of walking is effective in improving bowel function and body composition in the same patient population. The exploratory objectives are to address additional questions concerning the retention or non-retention of the positive changes, the effects of the increased physical activity from exoskeletal-assisted walking (WALK) on vagal tone, orthostatic tolerance, lipid profile, total testosterone, estradiol levels, and quality of life (QOL). Other tertiary goals are to explore the relationships among these variables. For example, if there is a change in HDL-c, total testosterone and estradiol levels, what is the relationship of this change with fat mass loss and/or is the magnitude of this change related to the achieved mobility and walking skills? The Primary and Secondary specific aims are supported with the pilot data and the exploratory aims are of interest and may be used to inform the investigators as to the feasibility and design of future work.

Key Words

- Exoskeletal Assisted Walking (EAW)
- Spinal Cord Injury (SCI)
- HDL-c
- Lipid profile
- Orthostatic tolerance
- Total testosterone
- Estradiol
- Quality of Life (QOL)
- ReWalk
- Ekso

Accomplishments

What were the major goals of the project?

The primary objectives of this proposal are to achieve successful walking skills in the exoskeletal-assisted walking devices for an extended period of time and at specific velocities and distances over the course of 36 sessions in three months in people with chronic SCI who are wheelchair dependent for community mobility. The secondary objectives are to determine if this amount of walking is effective in improving bowel function and body composition in the same patient population. Other tertiary goals are to explore the relationships among these variables.

Primary Aims: (100% success rate for participants completing WALK phase thus far)

1. By session 12 (first month of WALK training), the participants will be able to perform the following exoskeletal-assisted walking tests with or without minimal assistance:
    a. 10m WT
        i. 90% in ≤60 seconds (≥0.17 m/s)
        ii. 10% in ≤40 seconds (≥0.25 m/s)
    b. 6min WT
        i. 80% at a distance of ≥50 m (≥0.14 m/s)
        ii. 20% at a distance ≥80 m (≥0.22 m/s);
    c. TUG
        i. 80% in ≤120 seconds
        ii. 20% in ≤90 seconds

2. By session 36 (three months of WALK training), participants will have improved their ability to walk faster and longer distances and will be able to perform exoskeletal-assisted walking tests with or without minimal assistance as follows:
    a. 10m WT - 70% in ≤40 seconds (≥0.25 m/s)
    b. 6min WT - 70% at a distance ≥80 m (≥0.22 m/s)
    c. TUG - 60% in ≤90 seconds.

Secondary Aims are to affect the following by three months of exoskeletal-assisted walking (WALK): (These results have not been examined as no participant has completed the study thus far)

1. To improve bowel function as measured by established survey instruments; and
2. To reduce total body fat mass and percent fat as measured by DXA.

Exploratory Aims: (These results have not been examined as no participant has completed the study thus far)

1. To improve autonomic/cardiovascular function (vagal tone) measured by high frequency component of the 24-hour Holter monitor;
2. In persons with T6 and above, to improve orthostatic hypotension (OH) tolerance measured by a standard OH challenge test from supine to seated;
3. To improve HDL-c, Homeostatic Model of Assessment – Insulin Resistance (HOMA-IR), serum total testosterone and estradiol levels measured by serum and plasma assay kits; and
4. To improve quality of life (QOL) measured by item banks from the SCI-QOL and Patient Reported Outcomes Measurement Information System (PROMIS).

What was accomplished under these goals?

The study successfully commenced and research activities were started at all three study sites.

	Timeline	Research Sites		
	(Months)	**BVMRF/ JJPVAMC**	**UMROI**	**KFRC**
Major Task 1: Study start-up and continuation administrative functions				
Subtask 1: Prepare Regulatory Documents and Research Protocol	1-3	Complete (100%)	Complete (100%)	Complete (100%)
If Applicable, coordinate with Sites for CRADA* submission	n/a			
If Applicable, coordinate with Sites for material transfer agreements (MTAs) or clinical trial agreements (CTAs) submission	n/a			
If Applicable, coordinate with Sites for nondisclosure agreements (NDAs).	n/a			
If applicable, indicate time required for submission and exemption of an Investigational Device Exemption (IDE) application to the U.S. Food and Drug Administration	1-3	Complete (100%)	Complete (100%)	Complete (100%)
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	Complete (100%)	Complete (100%)	Complete (100%)
Finalize consent form & human subjects protocol	1-3	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate with Sites for Local IRBs** protocol submission	1-3	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate with Sites for University IRB** review	1-6	n/a	Complete (100%)	n/a
Coordinate with Sites for Military 2nd level IRB** review (ORP/HRPO)	1-6	Complete (100%)	Complete (100%)	Complete (100%)
Submit amendments, adverse events and protocol deviations as needed	As needed	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate with Sites for annual IRB** report for continuing review	Annually	Complete (100%)	Complete (100%)	Complete (100%)
*Milestone Achieved: Local IRB** approval at BVMRF, UMROI, and KFRC*	3	Complete (100%)	Complete (100%)	Complete (100%)
*Milestone Achieved: HRPO*** approval for all protocols and local IRB** approvals.*	6	Complete (100%)	Complete (100%)	Complete (100%)
Subtask 2: Coordinate with Sites for job descriptions design	1-3	Complete (100%)	Complete (100%)	Complete (100%)
Advertise and interview for project related staff	1-3	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate for space allocation for new staff	1-3	Complete (100%)	Complete (100%)	Complete (100%)

	Timeline	Research Sites		
	(Months)	**BVMRF/ JJPVAMC**	**UMROI**	**KFRC**
Coordinate with Sites for hiring and training of staff	1-6	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate with Sites for providing standard training procedures among exoskeletal-trainers	1-6	Complete (100%)	Complete (100%)	Complete (100%)
Milestone Achieved: Research staff hired and begin staff training	6	Complete (100%)	Complete (100%)	Complete (100%)
Subtask 3: Facilitate and Coordinate with Sites for hiring, training, supervision and fidelity checks as needed for study participant attrition	6-48	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate multi-site training meeting for exoskeletal training, walking assessments standardization, data collection paper forms, data collection web-based forms, and use of log record	3-6	Complete (100%)	Complete (100%)	Complete (100%)
PI, Lead Engineer and Study Coordinator travel to Sites for staff training of procedures	3-6	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate multi-site training meeting for standardization of SCI QOL and bowel function assessments	3-6	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate multi-site training meeting for blood draw procedures (fasting condition, amounts, tubes, mailing to Quest Diagnostics)	3-6	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate multi-site training meeting for orthostatic tolerance test and Holter monitor assessment	3-6	Complete (100%)	Complete (100%)	Complete (100%)
Coordinate with Sites for training to maintain 100% concordance with Study protocol	6-48	Complete (100%)	Complete (100%)	Complete (100%)
Milestone Achieved: Maintained trained Study staff throughout duration of the clinical trial	6-48	Complete (100%)	Complete (100%)	Complete (100%)
Major Task 2: Study recruitment and enrollment				
Subtask 1: Begin participant screening and consenting process	6-7	Complete (100%)	Complete (100%)	Complete (100%)
Milestone Achieved: Participant #1 consented, randomized and enrolled at each Site	6-7	Complete (100%)	Complete (100%)	Complete (100%)
Subtask 2: Randomize the first 4 participants at each respective Site	7-15	Complete (100%)	Complete (100%)	NYH
Complete participant baseline evaluations	7-15	Complete (100%)	Complete (100%)	Complete (100%)
Complete participant weekly and monthly evaluations	7-15	Complete (100%)	Complete (100%)	Complete (100%)
Complete participant post evaluations	7-15	Complete (100%)	Complete (100%)	Complete (100%)
Complete participant 1-month follow-up evaluations	10-15	Complete (100%)	Complete (100%)	Complete (100%)

	Timeline	Research Sites		
	(Months)	**BVMRF/ JJPVAMC**	**UMROI**	**KFRC**
Milestone Achieved: 12 participants consented, screened, randomized, and enrolled for the study	7-15	Complete (100%)	Complete (100%)	Complete (100%)
Subtask 3: Randomize the next 8/6/4 participants at each respective Site	16-24			
Complete participant baseline evaluations	16-24			
Complete participant weekly and monthly evaluations	16-24			
Complete participant post evaluations	16-24			
Complete participant 1-month follow-up evaluations	19-24			
Milestone Achieved: 30 participants consented, screened, randomized, and enrolled for the study	16-24			
Subtask 4: Randomize the next 8/6/4 participants at each respective Site	25-33			
Complete participant baseline evaluations	25-33			
Complete participant weekly and monthly evaluations	25-33			
Complete participant post evaluations	25-33			
Complete participant 1-month follow-up evaluations	28-33			
Milestone Achieved: 48 participants consented, screened, randomized, and enrolled for the study	25-33			
Subtask 5: Randomize the next 8/4/4 participants at each respective Site	34-42			
Complete participant baseline evaluations	34-42			
Complete participant weekly and monthly evaluations	34-42			
Complete participant Post 1 evaluations	34-42			
Complete participant Post 2 evaluations	34-42			
Complete participant 1-month follow-up evaluations	37-42			
Milestone Achieved: 64 participants consented, screened, randomized, and enrolled for the study	34-42			
Subtask 6: Complete training and testing of any remaining participants at each respective Site	43-45			
Complete participant weekly and monthly evaluations	43-45			
Complete participant post evaluations	43-45			
Milestone Achieved: All participants at each respective Site completed	43-45			

	Timeline	Research Sites		
	(Months)	BVMRF/ JJPVAMC	UMROI	KFRC
Major Task 3: Review/complete data forms, data edits and entry				
Subtask 1: Ongoing review of data entry	7-45			
Subtask 2: Ongoing review of adverse and serious adverse events	6-45			
Subtask 3: Ongoing data edits for missing values	7-45			
Subtask 4: Ongoing review for data entry errors	7-45			
Subtask 5: Complete all data entry	43-45			
Milestone Achieved: Data entry is completed in the data base	45			
Major Task 4: Review and analyze data				
Subtask 1: Review of data / analyze data	7-15			
Review data for problems	7-15			
Make necessary protocol adjustments (if needed)	7-15			
Perform sub analyses of walking tests and activity logs in first 12 participants	15-16			
Milestone Achieved: Data reviewed for necessary adjustment	7-15			
Subtask 2: Analyze preliminary data for primary outcomes	24-38			
Perform sub analyses of walking tests and activity logs in the first 20 to 38 participants	24-38			
Subtask 2: Submit abstracts with preliminary data for primary outcomes for national meetings	24-38			
Milestone Achieved: Abstract presentations of preliminary data	28-38			
Subtask 3: Analyze preliminary data for secondary outcomes	24-40			
Perform sub analyses of 1-month follow-up of bowel function assessments in the first 30 to 48 participants	24-36			
Perform sub-analyses of body fat mass in the first 30 to 48 participants	24-40			
Subtask 4: Analyze preliminary data for exploratory outcomes	15-36			
In Group 1, perform sub analyses of bowel function for one-month follow-up in the first 15 to 24 participants	15-24			GFF
In Group 1, perform sub analyses of body fat mass at 3 months follow-up in first 15 to 24 participants	15-24			GFF
Perform sub analyses of blood pressure tests and Holter monitor in the first 30 to 48 participants	25-36			GFF

	Timeline	Research Sites		
	(Months)	**BVMRF/ JJPVAMC**	**UMROI**	**KFRC**
Perform sub analysis of lipids, and endocrine outcome variables in the first 30 to 48 participants	25-36			
Perform sub analyses of SCI-QOL and bowel function assessments in first 30 to 48 participants	25-36			
Major Task 5: Prepare and write manuscripts				
Subtask 1: Prepare and write manuscripts on full data set of participants	43-48			
Prepare and write manuscript of the primary outcomes	43-48			
Prepare and write manuscript of the secondary outcomes	43-48			
Prepare and write manuscripts for the exploratory outcomes	43-48			

Enrollment goals were met at each site:

- JJPVAMC – 5 participants enrolled (4 anticipated)
- UMROI – 4 participants enrolled (4 anticipated)
- KIR – 4 participants enrolled (4 anticipated)

Results and key outcomes are being actively collected and updated. At this time (September 30, 2014), although the enrollment goals are being met, the data is not sufficient for analysis. An interim analysis is anticipated after the next six to nine months. However, the Primary outcome may only be analyzed with the full sample. All data will be collectively analyzed at the completion of the study.
Of the 13 enrolled participants to date, one had discontinued enrollment due to a medical reason, leaving 92% in the study.

Primary Aims:
Ninety-two percent of the participants reached either the targeted time points of the study design. Measurements were recorded, stored, and are to be analyzed collectively at study completion.

Secondary Aims:
Measurements were obtained and stored successfully from all active participants (92%). Data will be analyzed collectively at the completion of the study.

Exploratory Aims:
Measurements for 24 Hour Holter, OH challenge, phlebotomy, and QOL surveys were obtained successfully during the pre and crossover time points for 92% of the participants. Data will be analyzed collectively at study completion.

What opportunities for training and professional development has the project provided?
Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
All three sites will continue recruitment of participants to meet recruitment goals. The first group of enrollees will have neared completion by the next reporting period. Any study-related issues will be reviewed and reported.

Impact

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report

What was the impact on other disciplines?
Nothing to report

What was the impact on technology transfer?
Nothing to report

What was the impact on society beyond science and technology:
Nothing to report

Changes/Problems

Changes in approach and reasons for change:
To increase the recruitment of veterans from the patient population, the study age limit was raised from 65 years of age to 70 years of age. This slight increase of age posed no greater risk to the patient population as screening/randomization criteria were not modified.

Actual or anticipated problems or delays and actions or plans to resolve them:
Nothing to report

Changes that had a significant impact on expenditures:
Nothing to Report

Significant changes in use or care of human subjects:
Nothing to report

Products

Publications, conference papers, and presentations:
Nothing to report

Websites or other Internet sites:
Nothing to report

Technologies or techniques:
Nothing to report

Inventions, patent applications, and/or licenses:
Nothing to report

Participants & Other Collaborating Organizations

What individuals have worked on the project:
JJPVAMC:
Ann M. Spungen, EdD: no change
Manuel Avedissian, MD: no change
Pierre Asselin, MS: no change
Steven Knezevic, MS: no change
Stephen Kornfeld, DO: no change
Denis Doyle-Green: no change
Runlin Zhang, MD: no change
Jill M. Wecht, EdD: no change
William A. Bauman, MD: no change
Noam Y. Harel, MD, PhD: no change

UMROI:
Peter H Gorman, MD: no change
Paula Geigle, PhD: no change
William Scott, MA: no change
Leigh Casey: no change
Marni Kallins, PT: no change
John Perreault, CRNP: no longer on study

KIR:
Gail Forrest, PhD: no change
Steven Kirshblum, MD: no change
LeighAnn Martinez: no change
Christopher Cirnigliaro, MS: no change
Ryan Lamb: no longer on study
Erica Garbrini, PT: no longer on study

What other organizations were involved as partners:

- University of Maryland Rehabilitation and Orthopaedic Institute
  - 2200 Kernan Dr. Baltimore, MD 21207
  - Secondary site

- Kessler Institute for Rehabilitation
  - 1199 Pleasant Valley Way, West Orange, NJ 07052
  - Secondary and Facilities site

Special Reporting Requirements (N/A)

Collaborative Awards:
Nothing to report

Quad Charts:
(Please see attached form)

Appendices

Nothing to report

A Randomized, Crossover Clinical Trial of Exoskeletal-assisted Walking to Improve Mobility, Bowel Function and Cardio-Metabolic Profiles in Persons with SCI

Insert ERMS/Log Number and Task Title (Unknown)

SC130234

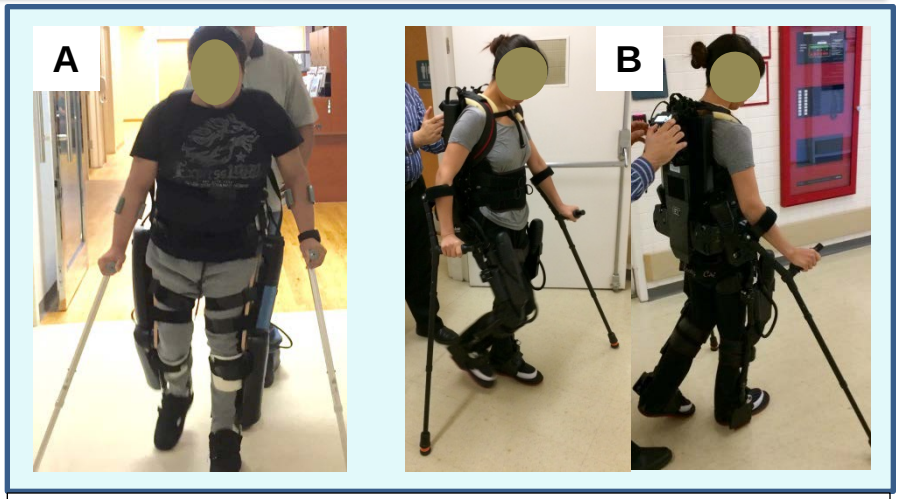
PI: Dr. Ann M. Spungen **Org:** Bronx Veterans Medical Research Foundation **Award Amount:** $1,555,889

Study/Product Aim(s)

The **primary objectives** are to achieve successful walking skills in the exoskeletal-assisted walking devices for an extended period of time and at specific velocities and distances over the course of 36 sessions in three months in people with chronic SCI who are wheelchair dependent for community mobility. The **secondary objectives** are to determine if this amount of walking is effective in improving bowel function and body composition.

Approach

A two-group, Phase III randomized clinical trial (RCT) is being performed using a crossover design with an exoskeletal-assisted walking intervention. Group 1 serves as the intervention follow-up to assess retention/non-retention of change due to the intervention on the outcome variables. Group 2 will serve as a lead-in to assess stability of the outcome variables prior to the intervention.



Panel A – Participant with motor incomplete paraplegia (T11, AIS D) walking in the ReWalk exoskeleton. Panel B - Participant with motor complete paraplegia (T3, AIS A) walking in the Ekso exoskeleton.

Timeline and Cost

Activities	FY 16	17	18	19
Text (12 participants enrolled)	Completed			
Text (18 participants to be enrolled)				
Text (18 participants to be enrolled)				
Text (16 participants to be enrolled)				
Estimated Budget ($K)	**$352**	**$371**	**$381**	**$263**

Updated: (November 25, 2015)

Goals/Milestones

FY16 Goals – Startup, kick-off and training meetings at each site; Initiate participant enrollment

☑ Q3-Participant screening and enrollment of 4 participants/site.

FY17 Goal – Continued participant screening and enrollment

❑ Q2-Participant screening, recruitment and enrollment of 8 (JJPVAMC), 4 (KF) and 6 (UMROI) participants per respective sites.

FY18 Goal – Continued enrollment

☐ Q1-Participant enrollment of 8 (JJPVAMC), 4 (KF) & 6 (UMROI)

☐ Q4-Participant enrollment of 8 (JJPVAMC), 4 (KF) & 4 (UMROI)

FY19 Goal – Completion of data collection

☐ Q2-Completion of participants

☐ Q3 to Q4 -Completion of data edits, analysis; Manuscript preparation

Comments/Challenges/Issues/Concerns - None

Budget Expenditure to Date

Projected Expenditure FY16 (Year 1): Approximate $352,335

Actual Expenditure FY16 (Year 1): Approximate $352,335